

12/B

### III. SUBMISSION UNDER 37 C.F.R. § 1.114(c)

The following amendment and response to the current office action are submitted under 37 C.F.R. § 1.114(c).

#### AMENDMENT

##### In the Claims:

Please amend the claims as follows:

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1. (Amended twice) A method comprising:
- a) obtaining at least a first soluble anti-nuclease antibody;
  - b) obtaining at least a second soluble anti-nuclease antibody;
  - c) obtaining a composition; and
  - d) admixing the anti-nuclease antibodies and the composition to form an admixture;

wherein nucleases that may be present in the admixture are inhibited.

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37. (Amended) A method of performing *in vitro* translation comprising obtaining a first nuclease inhibitor, which inhibitor is further defined as a soluble anti-nuclease antibody, and placing the anti-nuclease antibody in an *in vitro* translation reaction.

Please add the following new claims:

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56. (New) A method comprising:
- a) obtaining an anti-RNase antibody that binds to one or more members of the RNase A family;
  - b) obtaining an anti-RNase T1 antibody;
  - c) obtaining an anti-RNase 1 antibody;

- d) obtaining a composition; and
- e) admixing the anti-RNase antibodies and the composition to form an admixture;

wherein RNases that may be present in the admixture are inhibited.

57. (New) The method of claim 56, wherein admixing is further defined as comprising mixing the anti-RNase antibodies to form a nuclease inhibitor cocktail and mixing the nuclease inhibitor cocktail with the composition.

58. (New) The method of claim 56, wherein obtaining the anti-RNase antibodies comprises obtaining an RNase inhibitor cocktail comprising the anti-RNase antibodies.

59. (New) The method of claim 56, wherein the admixture comprises at least one nuclease.

60. (New) The method of claim 56, wherein the admixture comprises RNA.

61. (New) The method of claim 56, wherein the admixture is further defined as an *in vitro* translation reaction mixture, a transcription reaction mixture, a reverse transcription reaction mixture, or a coupled transcription/translation reaction mixture.

62. (New) The method of claim 56, wherein the composition is a reagent used in molecular biology.

63. (New) The method of claim 56, wherein at least one of the anti-RNase antibodies is a polyclonal antibody.

64. (New) The method of claim 56, further comprising obtaining a nuclease inhibitor and admixing the nuclease inhibitor with the composition wherein the nuclease inhibitor is human placental ribonuclease inhibitor, a bovine ribonuclease inhibitor, a porcine ribonuclease

inhibitor, diethyl pyrocarbonate, ethanol, formamide, guanidinium thiocyanate, vanadyl-ribonucleoside complexes, macaloid, sodium dodecyl sulfate, ethylenediamine tetraacetic acid, proteinase K, heparin, hydroxylamine-oxygen-cupric ion, bentonite, ammonium sulfate, dithiothreitol,  $\beta$ -mercaptoethanol, cysteine, dithioerythritol, tris (2-carboxyethyl) phosphene hydrochloride,  $Mg^{+2}$ ,  $Mn^{+2}$ ,  $Zn^{+2}$ ,  $Fe^{+2}$ ,  $Ca^{+2}$ , or  $Cu^{+2}$ .

65. (New) The method of claim 64, wherein the nuclease inhibitor is human placental ribonuclease inhibitor.

66. (New) The method of claim 56, further defined as a method of inhibiting nucleases in the admixture.

The claims marked for amendment are provided in Appendix A. For the Examiner's convenience, a clean copy of the pending claims as they stand amended is provided in Appendix B.

## RESPONSE

### A. Status of the Claims

Claims 1-50 were filed with the application. Claims 1-23 and 37-49 were elected in response to the restriction requirement of September 14, 2001. Claims 8, 17 and 22 were canceled without prejudice or disclaimer. Claims 1-7, 9-16, 18, 20, 23, 44 and 46 were amended and new claims 51-55 added by the amendment filed February 7, 2002. Claim 1 and claim 37 are amended and new claims 56-66 are added by the amendment herein. Therefore, claims 1-7, 9-16, 18-21, 23, 37-49, and 51-66 are pending. Applicants note that the numbering and dependencies of the pending claims may require correction upon allowance. However, Applicants have retained the original claim numbering so as to simplify discussion.

**B. Response to the Action's Response to Applicants' Arguments.**

The Action states that Applicants have argued against the rejections under 35 U.S.C. §103(a) by attacking the reference individually. The Action, page 11, lines 3-6. Applicants respectfully note that the cited statement incorrectly characterizes Applicants' arguments. The holding of *In re Royka*, 490 F.2d 981 (CCPA 1974) states that *all* of the claim limitations must be taught or suggested by the prior art. Thus, if one cited reference is devoid of a teaching or suggestion of a claim element, the element must be found in the balance of the references cited, so that as a whole, the cited art contains or suggests all the limitations of the claims. *Id.* Applicants merely pointed out in their earlier arguments what the Action admits, that there are elements of the claimed invention that are not disclosed or suggested by Lee *et al.* Therefore, in order to satisfy the legal standard of a *prima facie* case of obviousness, the balance of the references must contain or suggest the missing limitations. Applicants therefore pointed out that Cazenave (1977), Bucala *et al.* or Murphy *et al.* do not contain or suggest the missing limitations of the claims and that therefore the references taken together as a whole do not contain or suggest the present invention. These arguments are reiterated and amplified below.

**C. The rejections under 35 U.S.C. 103(a) are overcome.**

The Action rejects all the claims as obvious in view of Lee *et al.* in combination with Cazenave and Bucala *et al.* or Murphy *et al.* The Action, page 3, lines 1-4; page 6, lines 17-20; and page 8, lines 5-9. Applicants respectfully traverse these rejections.

Applicants respectfully submit that no valid *prima facie* case of obviousness may be made by any one of the cited references nor by their combination as a whole because all the limitations of the claims are not present in nor suggested by the cited references, taken as a

whole. Furthermore, taken as a whole, the references do not suggest the elements of the present invention nor their combination and cannot provide any reasonable expectation of success in making and using the invention as claimed.

**1. There is no suggestion in the cited art to make the present invention with any reasonable expectation of success.**

The Action argues that Lee *et al* provides “strong motivation” to make and use the present invention, citing the passage of Lee *et al*. suggesting improvements in the methods of purification of polysomes. The Action, page 11, lines 8-12. However, Applicants respectfully point out that the characterization of the content and import of the cited reference goes beyond the actual content of the reference. Furthermore, any suggestion must be accompanied by a reasonable expectation of success. Applicants have not found either the required suggestion to make and use the present invention nor the requisite reasonable expectation of success in the sum of the references cited.

The Action alleges that Lee *et al*. provides sufficient motive and expectation of success in making “any numbers and combinations of antibodies elicited against r-s-RNase and all other nucleases present in the crude tissue extract can be used in order to further improve the isolation of polysomes **as well as extraction of nucleic acids from any mixtures wherein nucleases may be present.**” The Action, page 11, lines 12-15, emphasis added. Applicants respectfully point out that Lee *et al*. does not go so far.

The scope of any suggestion and any reasonable expectation of success found in Lee *et al*. must come from the context of the work described and the skill of the ordinary artisan. In particular, the work reported in Lee *et al*. is expressly directed to the problem of isolation of

intact polysomes from whole tissue homogenates. The solution obtained by Lee *et al.*, as well as the further suggestion of an improved solution, are directed towards the isolation of polysomes from tissue homogenates. Indeed, The Action notes that the suggested method of inhibiting the nuclease of Lee *et al.* is to achieve the express advantages in the isolation of polysomes that may be further improved by the use of polyspecific immunosorbents. The Action page 6, lines 12-15. There is no teaching or suggestion in Lee *et al.* that the anti-nuclease antibodies contemplated by Lee *et al.* would be useful in any other context other than the isolation of polysomes from crude tissue homogenate. Nor is there any such suggestion to be found in the balance of Cazenave, Bucala *et al.*, or Murphy *et al.* There is therefore no suggestion to be found in the cited references as a whole. Nor would one be able to infer the Action's conclusions from the knowledge of the ordinary artisan.

Applicants also respectfully point out that Lee *et al.* teach away from the present invention. The anti-nuclease antibodies contemplated by Lee *et al.* are necessarily insolubilized. Lee *et al.* expressly do not use soluble antibodies, nor does the text suggest that soluble antibodies would be effective or useful in any of their disclosed or suggested methods. The methods disclosed by Lee *et al.* employ antibodies to rabbit spleen RNase (r-s-RNase) as a "reverse immunosorbent, prepared by polymerizing monospecific sheep antibodies to r-s-RNase with ethylene-maleic anhydride copolymer (EMA)." Lee *et al.*, page 210 lines 25-26 through page 211 line 1, internal quotes and referenced omitted. Thus, the antibodies disclosed by Lee *et al.* are rendered insoluble.

The necessity of insoluble antibodies to the methods of Lee *et al.* is made clear by the statement of prior success by Lee, *et al.* in that "[t]his immunosorbent was shown to be capable

of **removing** completely any free r-s-RNase (Lee and Schon, 1971)." Lee *et al.* page 211, lines 2-3, emphasis added. It is thus clear from the disclosure of Lee *et al.* that the methods contemplated are for removing nucleases from solution by their binding to insolubilized antibodies, i.e. the so-called reverse immunosorbents. Furthermore, the suggestion by Lee *et al.* to further improve the methods of polysome isolation contemplate not the addition of soluble anti-nuclease antibodies, but the use of additional, insolubilized antibodies, which would act in the same manner as disclosed for the anti r-s-RNase antibodies in removing the nucleases from solution. Lee *et al.* page 213, lines 3-7.

Even if the disclosure of Lee *et al.* is read in the most favorable light, the disclosure does not provide any data or reasoning to support the speculation that use of a mixture of **soluble antibodies** would be effective in achieving the present invention. Contrary to that speculation, Lee *et al.* expressly indicate that removal of the nucleases from solution is the means by which improved polysome isolation is achieved. That such removal is central to the methods of Lee *et al.* is indicated in part by the suggestion of Lee *et al.* that in order to achieve improved polysome isolation, the additional, polyspecific antibodies would have to be cross-linked with EMA to form a "polyspecific immunosorbent," which would then be expected to result in improved yields of polysomes. But more importantly, there is no data or suggestion in Lee *et al.* that the use of soluble anti nuclease antibodies would work to inhibit nucleases as presently claimed.

Therefore, not only does Lee *et al.* not provide the requisite suggestion to combine coupled with a reasonable expectation of success, its suggestion, read in light of its full text, Lee *et al.*, actually teaches away from the present invention, which expressly recites soluble anti-

nuclease antibodies as effective inhibitors of nucleases. That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness, even if all the elements of the invention are shown to be available in the art. *Winner Int'l. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000).

Nor does the balance of the references suggest the present invention or overcome the teaching away of Lee *et al.* As explained in Applicants' previous response and as reiterated below, Cazenave is not concerned with the use of anti nuclease antibodies to inhibit nucleases. Indeed, Cazenave is not concerned with nuclease activity at all, but rather the transfer of idiotypes from one episode of immunization to another. As explained previously and below, the unspecified RNase antigens of Cazenave are the only primary antigens used in creating antibodies Ab1 and, independently, Ab1'. The rest of the antigens used are antibodies themselves. At best Cazenave discloses that antibodies to some unspecified RNase can be made. But even so, no disclosure or suggestion that any of these antibodies would be effective in inhibiting nucleases is provided.

Bucala *et al.*, as explained previously and below, is not concerned with the binding of anti nuclease antibodies to active nucleases at all. In fact, all the nucleases bound to antibodies disclosed in Bucala *et al.* are *already denatured* through electrophoresis under reducing conditions. Therefore, no inference that the antibodies used by Bucala *et al.* could or would in fact inhibit any nuclease activity may be gleaned from its disclosure. Murphy *et al.*, though expressly addressing the use of RNase inhibitors in various reaction conditions, does not disclose or discuss the use of any antibodies whatsoever.



The disparate objectives and disclosures of the cited references thus do not come together to suggest to the ordinary artisan that one may make and practice the present invention, which is expressly directed to the inhibition of nuclease activity through methods employing at least two soluble anti nuclease antibodies. No fair reading, however strained, may find a suggestion of the present invention in the sum of the disclosures of the cited references. Indeed, *Lee et al.* and *Bucala et al.* teach away from the present invention. Applicants therefore respectfully submit that no *prima facie* case of obviousness has been made. Applicants therefore respectfully request that the rejections be withdrawn.

**2. The elements of the claimed invention are not found in the cited references as a whole.**

The Action admits that *Lee et al.* fails to teach or suggest anti RNase 1 antibodies, anti RNase T1 antibodies, anti-deoxyribonuclease antibodies, or antibodies capable of binding to micrococcal nuclease. The Action at page 5. Further, the Action notes that *Lee et al.* do not teach second and third nuclease inhibitors as anti-ribonuclease antibodies. *Id.* Therefore, the Action relies upon the disclosure of Cazenave to supply the missing elements of rejected claims 12, 13, 16, 18, 20, 23. However, contrary to the assertions in the Action, Cazenave does not disclose or suggest the elements of these claims.

In part, this deficiency is the result of an incorrect interpretation of the disclosure of Cazenave (1977). In the arguments that follow, Applicants respectfully point out the claim limitations missing from the cited references yet present in the rejected claims. Applicants also demonstrate that a correct reading of the Cazenave reference does not cure the admitted deficiencies of the other references.

First, claims 12 and 13 both expressly recite anti-RNase 1 antibodies as elements of the invention. However, the antibodies to ribonuclease disclosed in Cazenave are not disclosed to be directed to RNase 1. Rather, the antibodies created and disclosed by Cazenave are directed to an unspecified ribonuclease. The ribonuclease used by Cazenave is at most described as "ribonuclease." Cazenave, page 5122, column 1, last sentence extending into column 2. Nowhere in Cazenave is the exact identity of this RNase disclosed or even suggested.

Nor can the use of RNase 1 antibodies be inherent in the disclosure of Cazenave. For a reference to disclose via inherent properties, the reference "must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, (Fed. Cir. 1991) emphasis added. Yet the identity of the RNase of Cazenave cannot be determined. It is thus clearly not necessary that the RNase of Cazenave is RNase 1. Therefore, the antibodies of Cazenave cannot necessarily be antibodies to RNase 1.

In citing Cazenave, the Action appears to confuse the names of the antibodies generated in Cazenave with the name RNase 1. Applicants respectfully provide here clarification of the terminology of Cazenave.

The antibodies of Cazenave are designated "Ab1" to indicate that they are the first antibodies to be used in experiments directed to dissecting the idiotype regulation of antibody synthesis in rabbits. The "1" appended to the "Ab" solely indicates that status, not the identity of the ribonuclease to which the antibody reacts. See page 5122, Column 2, second and third paragraphs, and Figure 1.

Second, the "Ab2" and "Ab3" antibodies are antibodies that react against the Ab1 and Ab2 antibodies, respectively. Thus, Ab2 does not recognize or react with any ribonuclease.

Rather, Ab2 recognizes and reacts with the antibody named Ab1. Likewise, Ab3 is not disclosed to recognize or react with (let alone inhibit) any ribonuclease. Ab3 recognizes and reacts with the antibody named Ab2. See page 5122, Column 2, second and third paragraphs, and Figure 1. Therefore, neither Ab2, nor Ab3 can be construed in any sense to be ribonuclease inhibitors. Rather, they are carriers of idiotypes indicative of antibody responses. See the Discussion of Cazenave, generally.

Third, the Ab1' antibodies are antibodies synthesized by the same rabbits that had produced Ab3 antibodies to the Ab2. See Cazenave at page 5122, Column 2, paragraphs 2 and 3. Cazenave posits that the similarities of the idiotypes of Ab1' antibodies produced among these rabbits are a result of the idiotypic relationships and similarities of immune response and allotype among individual rabbits. It is this phenomenon, the idiotypic relationships of the various antibodies, that is disclosed by Cazenave. No mixture of anti-ribonuclease antibodies, *let alone* anti-RNase 1 antibodies is ever disclosed.

The Action further relies upon Cazenave as disclosing an anti-ribonuclease antibody "capable of binding to micrococcal nuclease" and cites page 5124, column 1, second paragraph in rejecting claim 16. Applicants respectfully point out that the cited paragraph of Cazenave discloses the existence of *antibodies to carbohydrates, not nucleases*, and therefore does not provide the necessary claim element to support a *prima facie* case of obviousness against claim 16.

The cited paragraph of Cazenave relates the personal communication of J. Urbain to the effect that similar results relating to the idiotypic relationships may be obtained using antibodies to carbohydrates. But, as explicitly stated by Cazenave in the cited passages (page 5124, Column 1, second paragraph) the antibodies were created to *Micrococcus carbohydrates*. To quote:

"They have obtained *anti-carbohydrate* Ab1' antibodies bearing idiotypic specificities similar to those of original *anti-carbohydrate* Ab1 antibodies." (Emphasis added.) There is no mention of micrococcal nuclease anywhere in the reference, and certainly not at the cited passage. To aid in the proper interpretation of this passage, Applicants have provided the abstract of the paper reporting the work by Urbain *et al.* (1997 Proc. Natl. Acad. Sci. U.S.A. 74:5126-30) as Appendix C, wherein the authors state "**Anticarbohydrate** antibodies (Ab1) were isolated from a rabbit...etc." (first sentence of abstract, emphasis added).

In sum, a proper reading of the Cazenave reference reveals that it does not disclose equivalent second and third nuclease inhibitors as anti-ribonuclease antibodies as asserted by the Action. There are, in fact, no mixtures of anti-RNase 1 antibodies disclosed by Cazenave, nor any mention of Micrococcal anti-ribonuclease. Cazenave, therefore, does not disclose the limitations of claims 12, 13 and 16 that are absent from the balance of the references. Cazenave cannot support a *prima facie* case of obviousness against the claims.

Further, claim 13, in addition to reciting an anti-RNase 1 antibody, also recites an anti-RNase T1 antibody. The Action has left unaddressed the subject matter of this claim but for the admission that Lee *et al.* does not disclose an anti-RNase T1 antibody (the Action at page 5, lines 7-8). The Action refers to Lee *et al.* as suggesting antibodies to all other nucleases present in crude tissue (the Action at page 5, lines 9-10). The Action therefore apparently asserts that crude tissue homogenate from freshly excised rabbit spleen necessarily contains RNase T1, a fungal enzyme. Specification at page 21, lines 21-24. The assertion that Lee *et al.* disclose expressly or inherently RNase T1 is, however, clearly contradicted by the knowledge of the ordinary artisan and unsupported by any cited reference or examiner's affidavit pursuant to MPEP 2144.03.

There is no basis for the argument that RNase T1, a fungal enzyme, would necessarily be present in the crude tissue homogenates of Lee *et al.*

Claims 11, 14, and 19 recite at least in part the limitation of an anti-RNase A antibody. The Action admits that Lee *et al.* and Cazenave do not disclose the presently claimed methods wherein the anti-ribonuclease antibody is an anti-RNase A antibody. The Action at page 7, lines 3-4. Nevertheless, the Action suggests that one of skill in the art would be motivated to combine the anti-RNase antibody of Bucala *et al.* (2000) with the alleged teachings of Lee *et al.* and Cazenave to result in a method of inhibiting nucleases.

But contrary to the argument of the Action, RNase activity, *per se*, is never at issue in the Bucala *et al.* reference. Indeed, the quoted passage from Bucala *et al.* itself expressly teaches away from such a combination. In the Bucala *et al.* reference, RNase proteins are described merely as indicators of the extent of dimerization promoted by glycotoxins. Bucala *et al.* used rabbit anti-RNase A antibodies conjugated to HRP to detect **denatured** RNase proteins in a western blot. Bucala *et al.* therefore expressly did not use anti-RNase A antibodies effective in inhibiting active RNase activity.

The Action cites Bucala *et al. et al.* for the disclosure of an anti-RNase A antibody. However, as discussed above, there is no disclosure in Bucala *et al. et al.* that the antibodies of Bucala *et al. et al.* would be effective to inhibit nuclease activity since the RNase proteins detected by the antibodies of Bucala *et al. et al.* were already denatured, that is, they had no activity to inhibit. Thus, Bucala *et al. et al.* in conjunction with Lee *et al.* does not enable the use of soluble anti-RNase A antibodies to inhibit the activities of active nucleases in solution and cannot support a *prima facie* case of obviousness against the claims.

The Action allegedly rejects claims 1-7, 9, 10, 12, 13, 15, 16, 18, 20, 21, 23, 37-49 and 51-55 under 35 U.S.C. §103(a) over Lee *et al.* in view of Cazenave and further in view of Murphy *et al. et al.* (1995). However, the Action states that the rejection of claims 1-5, 7, 9, 10, 12, 13, 15, 16, 18, 20 and 23 is based entirely upon those grounds of rejection asserted over solely Lee *et al.* and Cazenave. The Action, page 8, lines 10-11. Therefore, Applicants read the rejection to indicate that the argument for rejection based upon Lee *et al.*, Cazenave, and Murphy *et al. et al.* is directed to claims 21, 37-49 and 51-55. Applicants respectfully traverse the rejections.

Applicants respectfully submit that no *prima facie* case of obviousness has been made against the claims because Murphy *et al. et al.* leads the artisan away from the present invention in that Murphy *et al. et al.* counters any reasonable expectation of success. Applicants therefore submit that the rejections are overcome.

Applicants agree with the arguments of the Action to the extent that Lee *et al.* in view of Cazenave do not disclose or suggest the limitations of claims 37-49 and 52-54, which contain the express limitations of a method of performing an in vitro translation. Applicants also agree that Lee *et al.* in view of Cazenave does not disclose or suggest human placental ribonuclease inhibitor. But further, as argued above, Lee *et al.* in view of Cazenave do not disclose or suggest a method of performing in vitro translation comprising obtaining a first nuclease inhibitor, which inhibitor is further defined as a soluble anti-nuclease antibody, and placing the anti-nuclease antibody in an in vitro translation reaction.

Nor does Murphy *et al. et al.* provide any suggestion of the presently claimed methods. Murphy *et al. et al.* does not disclose the use of any antibodies whatsoever. The Murphy *et al. et al.* reference does not disclose the use of antibodies in any situation, and most especially

not in *in vitro* translation reactions. Furthermore, there is no suggestion in Lee *et al.* that antibodies would work to remove nucleases from an *in vitro* transcription or other reaction mixture beyond that disclosed by Lee, i.e. crude tissue homogenates. And, as argued above, Lee *et al.* in view of any of the cited references does not provide for soluble anti-nuclease antibodies effective as inhibitors of nucleases. Therefore, there is no basis for an artisan of ordinary skill to conclude from these references that the addition of soluble anti-ribonuclease antibodies to a reaction mixture such as an *in vitro* transcription reaction would perform as desired.

In fact, Murphy *et al. et al.* discloses that "An extremely important feature of a RNase inhibitor" for use in such reactions is "that it remain fully functional under the various conditions to which RNA may be subjected." See Murphy *et al. et al.*, under "Reaction Parameters," first paragraph, lines 1-3. Yet, there is no demonstration or suggestion in any of Lee *et al.* or Murphy *et al. et al.* that anti-ribonuclease antibodies could withstand the various conditions as disclosed in the Murphy *et al. et al.* reference and be effective to inhibit nucleases. Absent such a suggestion from any reference and from the knowledge of one of skill in the art, Murphy *et al. et al.* only teaches away from the present invention. Murphy *et al.* raises numerous barriers to be crossed before achieving a successfully useful RNase inhibitor rather than enabling the ordinary artisan to make and use the present invention as claimed. That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness, even if all the elements of the invention are shown to be available in the art. *Winner Int'l. Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-50 (Fed. Cir. 2000).

Additionally, and as argued above, none of the references alone or in combination provide or suggest the specific limitations of these rejected claims. Here, in particular, Applicants point out that the method of claim 54, which expressly recites the use of three anti-

nuclease antibodies in an in vitro translation: an anti-RNase A antibody, an anti-RNase 1 antibody, and an anti-RNase T1 antibody, is nowhere disclosed or suggested in the art.

Furthermore, Applicants note that no specific grounds for rejecting claims 51 and 55 have been provided. Claim 51 recites the inclusion of at least a third anti-nuclease antibody, which binds to one or more of RNase A, a member of the RNase A family, RNase B, RNase C, RNase 1, RNase T1, RNase T2, RNase L, a member of the RNase H family, a member of the angiogenin RNase family, eosinophil RNase, a micrococcal nuclease, a member of the mammalian ribonuclease 1 family, a member of the ribonuclease 2 family, a messenger RNA ribonuclease, 5'-3' exoribonuclease, 3'-5' exoribonuclease, a decapping enzyme, a deadenylase, RNase P, RNase III, RNase E, RNase I,I\*, RNase HI, RNase HII, RNase M, RNase R, RNase IV, F; RNase P2,O, PIV, PC, RNase N, RNase II, PNPase, RNase D, RNase BN, RNase T, RNase PH, OligoRNase, RNase R, RNase Sa, RNase F1, RNase U2, RNase Ms, or RNase St. But nowhere in the cited references is there to be found the suggestion or provision of at least a third anti-nuclease antibody as claimed.

Claim 55 recites the express limitation that RNA be produced in the admixture of the method comprising at least a first soluble anti-nuclease antibody, obtaining at least a second soluble anti-nuclease antibody, obtaining a composition, and admixing the anti-nuclease antibodies and the composition to form an admixture comprising RNA, wherein nucleases that may be present in the admixture are inhibited. Applicants have seen nothing in the record or in the text of the rejections as stated that suggest that claim 55 is present in or obvious over the art.

Applicants respectfully submit that no *prima facie* case of obviousness has been made against the claims. Applicants therefore submit that the rejections are overcome.



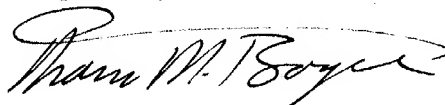
**D. New claims 56-66 are novel and non-obvious.**

The present amendment adds claims 56-66, which more particularly claim the present invention. In particular, claims 56-66 expressly recite a method comprising obtaining an anti-RNase antibody that binds to one or more members of the RNase A family, obtaining an anti-RNase T1 antibody; obtaining an anti-RNase 1 antibody; obtaining a composition; and admixing the anti-RNase antibodies and the composition to form an admixture wherein RNases that may be present in the admixture are inhibited. As argued above, this combination of elements is nowhere to be found or suggested in the art.

**IV. CONCLUSION**

In light of the foregoing amendments and remarks, applicants respectfully submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. Should the examiner have any questions regarding this response, and call to the undersigned is invited.

Respectfully submitted,



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